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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 **:**
A61K 31/57, 31/575, 31/56

A1

(11) International Publication Number: **WO 99/32127**

(43) International Publication Date: 1 July 1999 (01.07.99)

(21) International Application Number: PCT/US98/25913

(22) International Filing Date: 7 December 1998 (07.12.98)

(30) Priority Data:
08/994,114 19 December 1997 (19.12.97) US

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(81) Designated States: AU, BR, CA, JP, MX, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: ANGIOSTATIC AGENTS AND COMPOSITIONS FOR CONTROLLING OCULAR HYPERTENSION

(57) Abstract

Compositions of angiostatic agents for treating GLC1A glaucoma and methods for their use are disclosed.

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ANGIOSTATIC AGENTS AND COMPOSITIONS FOR CONTROLLING OCULAR HYPERTENSION

This is a continuation-in-part of an application entitled "Angiostatic Steroids and Methods and Compositions for Controlling Ocular Hypertension" filed on December 15, 1997, which is continuation of Serial No. 08/643,387 filed May 6, 1996 (issuing December 16, 1997, Patent No. 5,698,545), which is a continuation of Serial No. 08/349,342 filed December 2, 1994, which is a continuation of U. S. Patent No. 5,371,078 issued December 6, 1994, which is a continuation-in-part of Serial No. 07/559,123 filed July 27, 1990, which is a continuation-in-part of Serial No. 07/419,226 filed October 10, 1989, which is a continuation of Serial No. 07/264,918 filed October 31, 1988 (U.S. Patent No. 4,876,250).

Background of the Invention

Field of the Invention

This invention is directed to the use of angiostatic agents for treating glaucoma or ocular hypertension resulting from altered expression of the GLC1A gene (hereinafter GLC1A or 1q glaucoma) in an individual.

Description of Related Art

The glaucomas are a heterogeneous group of optic neuropathies characterized by cupping of the optic nerve head, thinning of the retinal nerve fiber layer due to loss of retinal ganglion cells, and specific pathognomonic changes in visual fields. Elevated intraocular pressure (IOP) is a very important risk factor for the development of most common forms of glaucoma (Sommer A, et al., "Relationship Between Intraocular Pressure and Primary Open Angle Glaucoma Among White and Black Americans," *Arch. Ophthalmol.*, 109:1090-1095, (1991)).

A family history of glaucoma also is an important risk factor for the development of glaucoma. It appears that a significant portion of glaucoma is inherited (or at least the risk for developing glaucoma is inherited) although it is often difficult to establish clear inheritance patterns for most of the glaucomas because of the disease onset late in life and the slowly progressive clinical manifestations of the disease. Despite these problems, a number of families with heritable forms of glaucoma have been identified and these families have been used to map

a variety of glaucoma genes (Sheffield, et al., "Genetic Linkage of Familial Open Angle Glaucoma to Chromosome 1q21-q31," *Nature Genetics*, 4:47-50 (1993); Sarfarazi, et al., "Assignment of a Locus (GLC3A) for Primary Congenital Glaucoma (Buphthalmos) to 2p21 and Evidence for Genetic Heterogeneity," *Genomics*, 30:171-177 (1995); Akarsu, et al., "A Second Locus (GLC3B) for Primary Congenital Glaucoma (Buphthalmos) Maps to the 1p36 Region," *Human Molecular Genetics*, 5(8):1199-1203 (1996); Stoilova, et al., "Localization of a Locus (GLC1B) for Adult-Onset Primary Open Angle Glaucoma to the 2cen-q13 Region," *Genomics*, 36:142-150 (1996); Wirtz, et al., "Mapping a Gene for Adult-Onset Primary Open-Angle Glaucoma to Chromosome 3q," *Am. J. Hum. Genet.*, 60:296-304 (1997); Andersen, et al., "A Gene Responsible for the Pigment Dispersion Syndrome Maps to Chromosome 7q35-q36," *Arch. Ophthalmol.*, 115:384-388 (1997). The first glaucoma gene mapped (GLC1A) was in a large family with autosomal dominant inherited juvenile glaucoma (JG). This disease is characterized by an early disease onset (late teens to early 20s), relatively high IOPs, and general resistance to conventional pharmacological IOP lowering therapy. The GLC1A gene was mapped by positional cloning and linkage analysis to chromosome 1q22-q25 (Sheffield et al, *Id.*), and a number of other groups have confirmed the 1q location of this juvenile glaucoma gene (Richards, et al., "Mapping of a Gene for Autosomal Dominant Juvenile-Onset Open-Angle Glaucoma to Chromosome 1q," *Am. J. Hum. Genet.*, 54:62-70 (1994); Morissette, et al., "A Common Gene for Juvenile and Adult-Onset Primary Open-Angle Glaucomas Confined on Chromosome 1q," *Am. J. Hum. Genet.*, 56:1431-1442 (1995); Wiggs, et al., "Genetic Linkage of Autosomal Dominant Juvenile Glaucoma to 1q21-q31 in Three Affected Pedigrees," *Genomics*, 21:299-303 (1994); Meyer, et al., "Age-Dependent Penetrance and Mapping of the Locus for Juvenile and Early-Onset Open-Angle Glaucoma on Chromosome 1q (GLC1A) in a French Family," *Hum. Genet.*, 98:567-571 (1996); Graff, et al., "Confirmation of Linkage to 1q21-31 in a Danish Autosomal Dominant Juvenile-Onset Glaucoma Family and Evidence of Genetic Heterogeneity," *Hum. Genet.*, 96:285-289 (1995). Glaucoma due to the GLC1A gene is often referred to as 1q glaucoma.

The GLC1A gene was identified as encoding a 57 kD protein expressed in the trabecular meshwork (TM) (Stone, et al., "Identification of a Gene That Causes Primary Open Angle Glaucoma," *Science*, 275:668-670 (1997). The expression of the GLC1A gene, and the encoded TM protein, is up-regulated by glucocorticoids (Polansky, et al., "Eicosanoid Production and Glucocorticoid Regulatory Mechanisms in Cultured Human Trabecular Meshwork Cells," *The*

Ocular Effects of Prostaglandins and Other Eicosanoids, pp. 113-138 (1989); Polansky, et al., "*In Vitro* Correlates of Glucocorticoid Effects on Intraocular Pressure," *Glaucoma Update IV* (1991); and Polansky, et al., "Cellular Pharmacology and Molecular Biology of the Trabecular Meshwork Inducible Glucocorticoid Response Gene Product," *Ophthalmologica*, 211:126-139 (1997)). This TM protein is also known as TIGR (trabecular meshwork inducible glucocorticoid response) (Polansky, *Id.)*. The glucocorticoid-induction of this TM protein has been suggested to be involved in the generation of glucocorticoid-induced ocular hypertension and glaucoma (Polansky, *Id.*).

The GLC1A gene is expressed in other ocular tissues such as the ciliary epithelium (Ortego, et al., "Cloning and Characterization of Subtracted cDNAs from a Human Ciliary Body Library Encoding TIGR, a Protein Involved in Juvenile Open Angle Glaucoma with Homology to Myosin and Olfactomedin," *FEBS Letters*, 413:349-353 (1997)) and the retina (Kubota, et al., "A Novel Myosin-like Protein (Myocilin) Expressed in the Connecting Cilium of the Photoreceptor: Molecular Cloning, Tissue Expression, and Chromosomal Mapping," *Genomics*, 41:360-369 (1997)). The gene is referred to by several names including GLC1A (Sheffield, *supra*; Sunden, et al., "Fine Mapping of the Autosomal Dominant Juvenile Open Angle Glaucoma (GLC1A) Region and Evaluation of Candidate Genes," *Genome Research*, 6:862-869 (1996); Stone, et al., *supra*), TIGR (Polansky *supra*; Ortego, *supra*), and myocilin (Kubota, *supra*). Mutations GLC1A are not only responsible for juvenile glaucoma, but also a significant subset of adult onset primary open angle glaucoma (Stone, et al., *supra*; Adam, et al., "Recurrent Mutations in a Single Exon Encoding the Evolutionarily Conserved Olfactomedin-Homology Domain of TIGR in Familial Open-Angle Glaucoma," *Human Molecular Genetics*, 6(12):2091-2097 (1997)). The 1q glaucoma gene (GLC1A, TIGR) is the subject of Nguyen, et al., U.S. Patent No. 5,606,043, issued February 25, 1997.

Glucocorticoids have been associated with the development of ocular hypertension and primary open angle glaucoma (Kass, et al., "Corticosteroid-Induced Glaucoma, In Ritch, R., Shields, M. B., Krupin, T. (eds.)," *The Glaucomas*, The C. V. Mosby Company, St. Louis, MO, pp. 1161-1168 (1989); DeSantis, et al., "Dexamethasone-Induction of Ocular Hypertension in the Primate, *ARVO Abstracts. Invest. Ophthalmol. Vis. Sci.,* 31(Suppl.):99 (1990); Knepper, et al., "Intraocular Pressure and Glycosaminoglycan Distribution in the Rabbit Eye: Effect of Age and Dexamethasone," *Exp. Eye Res.,* 27: 567-575 (1978); Francois, et al., "Ultrastructural and Morphometric Study of

Corticosteroid Glaucoma in Rabbits, *Ophthalmic Res.,* 16:168-178 (1984); Lorenzetti, O. J., "Effects of Corticosteroids on Ocular Dynamics in Rabbits," *J. Pharmacol. Exp. Therap.,* 175:763-772 (1970); and Zhan, et al., "Steroid Glaucoma: Corticosteroid-Induced Ocular Hypertension in Cats," *Exp. Eye Res.,* 54:211-218 (1992)). Glaucoma patients have also been reported to have higher levels of the endogenous glucocorticoid, cortisol (Rozsival, et al., "Aqueous Humour and Plasma Cortisol Levels in Glaucoma and Cataract Patients," *Current Eye Research,* 1:391-396 (1981); Ray, et al., "Plasma Cortisol in Glaucoma," *Ann. Ophthalmol.,* 9:1151-1154 (1977); and Schwartz, et al., "Increased Plasma Free Cortisol in Ocular Hypertension and Open Angle Glaucoma," *Arch. Ophthalmol.,* 105:1060-1065 (1987)).

It is known that trabecular meshwork cells have glucocorticoid receptors and that glucocorticoid binding with these receptors causes a change in trabecular meshwork cell gene expression. Known manifestations of this change include a reorganization of the cytoskeleton (Wilson, et al., "Dexamethasone Induced Ultrastructural Changes in Cultured Human Trabecular Meshwork Cells, *Cur. Eye Res.,* 12:783-793 (1993), and Clark, et al., "Glucocorticoid-Induced Formation of Cross-Linked Actin Networks in Cultured Human Trabecular Meshwork Cells," *Invest. Ophthalmol. Vis. Sci.,* 35:281-294 (1994)) and increased deposition of the extracellular matrix material in trabecular meshwork cells. As a result, the trabecular meshwork becomes "clogged" and unable to perform one of its most critical functions, that is, serving as a gateway for aqueous humor flow from the anterior chamber of the eye. When the aqueous humor flow out of the eye via the trabecular meshwork is diminished, the intraocular pressure of the eye rises. If this state of elevated intraocular pressure is maintained or frequently occurs, the optic nerve head can be damaged resulting in the loss of visual field. Loss of visual field is the hallmark symptom associated with glaucoma.

Endogenous glucocorticoids may be responsible for producing the changes in the trabecular meshwork that lead to ocular hypertension and glaucoma.

In summary, the GLC1A gene product can lead to the development of ocular hypertension and glaucoma in one of two ways: (1) mutations in GLC1A are responsible for most forms of juvenile glaucoma and a subset of adult onset POAG or (2) exposure of some individuals to glucocorticoids leads to increased GLC1A expression in the TM which causes increased aqueous

humor outflow resistance and the development of ocular hypertension. The precise mechanism(s) responsible for GLC1A effects on IOP are currently unknown.

Steroids functioning to inhibit angiogenesis in the presence of heparin or specific heparin fragments are disclosed in Crum, et al., "A New Class of Steroids Inhibits Angiogenesis in the Presence of Heparin or a Heparin Fragment," *Science*, 230:1375-1378 (December 20, 1985). The authors refer to such steroids as "angiostatic" steroids. Included within the new class of steroids found to be angiostatic are the dihydro and tetrahydro metabolites of cortisol and cortexolone. In a follow-up study directed to testing a hypothesis as to the mechanism by which the steroids inhibit angiogenesis, it was shown that heparin/angiostatic steroid compositions cause dissolution of the basement membrane scaffolding to which anchorage dependent endothelia are attached resulting in capillary involution; see, Ingber, et al., "A Possible Mechanism for Inhibition of Angiogenesis by Angiostatic Steroids: Induction of Capillary Basement Membrane Dissolution," *Endocrinology,* 119:1768-1775 (1986).

A group of tetrahydro steroids useful in inhibiting angiogenesis is disclosed in International Patent Application No. PCT/US86/02189, Aristoff, et al., (The Upjohn Company). The compounds are disclosed for use in treating head trauma, spinal trauma, septic or traumatic shock, stroke and hemorrhage shock. In addition, the patent application discusses the utility of these compounds in embryo implantation and in the treatment of cancer, arthritis and arteriosclerosis. The compounds are not disclosed for ophthalmic use.

Tetrahydrocortisol (THF) has been disclosed for its use in lowering the intraocular pressure (IOP) of rabbits made hypertensive with dexamethasone alone, or with dexamethasone/5-beta-dihydrocortisol; see Southren, et al., "Intraocular Hypotensive Effect of a Topically Applied Cortisol Metabolite: 3-alpha, 5-beta-tetrahydrocortisol," *Investigative Ophthalmology and Visual Science*, 28 (May, 1987). The authors suggest THF may be useful as an antiglaucoma agent. In U.S. Patent No. 4,863,912, issued to Southren et al. on September 5, 1989, pharmaceutical compositions containing THF and a method for using these compositions to control intraocular pressure are disclosed. THF has been disclosed as an angiostatic steroid in Folkman, et al., "Angiostatic Steroids," *Ann. Surg.*, 206(3) (1987) wherein it is suggested angiostatic steroids may have potential use for diseases dominated by abnormal

neovascularization, including diabetic retinopathy, neovascular glaucoma and retrolental fibroplasia.

Summary of the Invention

Angiostatic steroids and their pharmaceutical formulations are useful for treating GLC1A glaucoma. The invention is also directed to methods for controlling GLC1A glaucoma using angiostatic steroids.

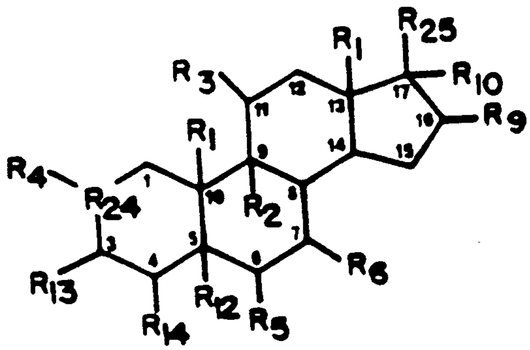
Detailed Description of Preferred Embodiments

Agents which alter the expression of GLC1A in the glaucomatous eye are expected to lower IOP and thereby prevent or inhibit the glaucomatous optic neuropathy which is being driven by elevated IOP. Glucocorticoids upregulte GLC1A expression in the TM of certain individuals. There have been several reports of elevated levels of the natural glucocorticid cortisol in the aqueous humor and plasma of glaucoma patients (Schwartz, et al., *supra*; Rozsival, et al., *supra*). In addition, certain mutations in GLC1A may alter the expression of GLC1A in the TM tissue of 1q glaucoma patients. Unexpectedly, it has been discovered that angiostatic agents inhibit the expression of GLC1A in cultured human TM cells and lower elevated IOP in certain animal models of ocular hypertension. The compounds thereby prevent the expression of GLC1A and the subsequent development of ocular hypertension.

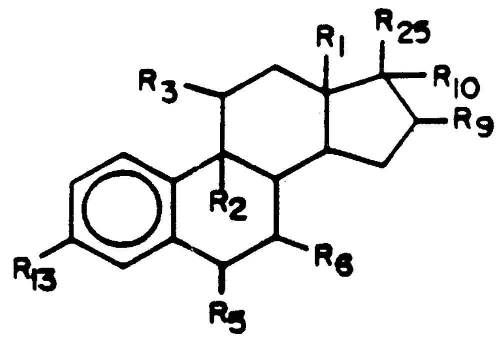
The development of blood vessels for the purpose of sustaining viable tissue is known as angiogenesis. Agents which inhibit angiogenesis are known by a variety of terms such as angiostatic, angiolytic or angiotropic agents. For purposes of this specification, the term "angiostatic agent" means compounds which can be used to inhibit angiogenesis.

The specific angiostatic agents of the present invention are steroids or steroid metabolites. For purposes herein, the term "angiostatic steroids" means steroids and steroid metabolites which inhibit angiogenesis. The present invention is based on the finding that angiostatic steroids can be used for the control of ocular hypertension. In particular, the agents can be used for the treatment of GLC1A glaucoma.

Preferred angiostatic steroids of the present invention have the following formula:



Structure [A]



Structure [B]

wherein R_1 is H, β-CH_3 or β-C_2H_5;

R_2 is F, C_9-C_{11} double bond, C_9-C_{11} epoxy, H or Cl;

R_3 is H, OR_{26}, $OC(=O)R_{27}$, halogen, C_9-C_{11} double bond, C_9-C_{11} epoxy, =O, -OH, -O-alkyl(C_1-C_{12}), -OC(=O)alkyl(C_1-C_{12}), -OC(=O)ARYL, $-OC(=O)N(R)_2$ or $-OC(=O)OR_7$, wherein ARYL is furyl, thienyl, pyrrolyl, or pyridyl and each of said moieties is optionally substituted with one or two (C_1-C_4)alkyl groups, or ARYL is $-(CH_2)_f$-phenyl wherein f is 0 to 2 and the phenyl ring is optionally substituted with 1 to 3 groups selected from chlorine, fluorine, bromine, alkyl(C_1-C_3), alkoxy(C_1-C_3), thioalkoxy-(C_1-C_3), Cl_3C-, F_3C-, $-NH_2$ and $-NHCOCH_3$ and R is hydrogen, alkyl (C_1-C_4), or phenyl and each R can be the same or different, and R_7 is ARYL as herein defined, or alkyl(C_1-C_{12});

R_4 is H, CH_3, Cl or F;

R_5 is H, OH, F, Cl, Br, CH_3, phenyl, vinyl or allyl;

R_6 is H or CH_3;

R_9 is $CH_2CH_2OR_{26}$, $CH_2CH_2OC(=O)R_{27}$, H, OH, CH_3, F, $=CH_2$, $CH_2C(=O)OR_{28}$,, OR_{26}, $O(C=O)R_{27}$ or $O(C=O)CH_2(C=O)OR_{26}$

R_{10} is $-C{\equiv}CH$, $-CH=CH_2$, halogen, CN, N_3, OR_{26}, $OC(=O)R_{27}$, H, OH, CH_3 or R_{10} forms a second

bond between positions C-16 and C-17;

R_{12} is H or forms a double bond with R_1 or R_{14};

R_{13} is halogen, OR_{26}, $OC(=O)R_{27}$, NH_2, NHR_{26}, $NHC(=O)R_{27}$, $N(R_{26})_2$, $NC(=O)R_{27}$, N_3, H, -OH, =O, -O-P(=O)$(OH)_2$, or -O-C(=O)-$(CH_2)_t$COOH where t is an integer from 2 to 6;

R_{14} is H or forms a double bond with R_{12};

R_{15} is H, =O or -OH;

and R_{23} with R_{10} forms a cyclic phosphate;

wherein R_9 and R_{15} have the meaning defined above;

or wherein R_{23} is -OH, O-C(=O)-R_{11}, -OP(O)-$(OH)_2$, or -O-C(=O)-$(CH_2)_t$COOH wherein t is an integer from 2 to 6; and R_{11} is -Y-$(CH_2)_n$-X-$(CH_2)_m$-SO_3H, -Y'-$(CH_2)_p$-X'-$(CH_2)_q$-$NR_{16}R_{17}$ or -Z$(CH_2)_r$Q,

wherein Y is a bond or -O-; Y' is a bond, -O-, or -S-; each of X and X' is a bond,-CON(R_{18})-, -N(R_{18})CO-, -O-, -S-, -S(O)-, or -S(O_2)-; R_{18} is hydrogen or alkyl (C_1-C_4); each of R_{16} and R_{17} is a lower alkyl group of from 1 to 4 carbon atoms optionally substituted with one hydroxyl or R_{16} and R_{17} taken together with the nitrogen atom to which each is attached forms a monocyclic heterocycle selected from pyrrolidino, piperidino, morpholino, thiomorpholino, piperazino or N(lower)alkyl-piperazino wherein alkyl has from 1 to 4 carbon atoms; n is an integer of from 4 to 9; m is an integer of from 1 to 5; p is an integer of from 2 to 9; q is an integer of from 1 to 5;

Z is a bond or -O-; r is an integer of from 2 to 9; and Q is one of the following:

(1) -R_{19}-CH_2COOH wherein R_{19} is -S-, -S(O)-, -S$(O)_2$-, -SO_2N(R_{20})-, or N(R_{20})SO_2-; and R_{20} is hydrogen or lower alkyl-(C_1-C_4); with the proviso that the total number of carbon atoms in R_{20} and $(CH_2)_r$ is not greater than 10; or

(2) -CO-COOH; or

(3) CON(R_{21})CH(R_{22})COOH wherein R_{21} is H and R_{22} is H, CH_3, -CH_2COOH, -CH_2CH_2COOH, -CH_2OH, -CH_2SH, -$CH_2CH_2SCH_3$, or -CH_2Ph-OH wherein Ph-OH is p-hydroxyphenyl;

or R_{21} is CH_3 and R_{22} is H;

or R_{21} and R_{22} taken together are -$CH_2CH_2CH_2$-;

or -N(R_{21})CH(R_{22})COOH taken together is -NHCH_2CONHCH_2COOH; and pharmaceutically acceptable salts thereof;

with the proviso that if R_{23} is a phosphate, it must form a cyclic phosphate, with R_{10} when R_{13} is =O, except for the compound wherein R_1 is β-CH_3, R_2 and R_3 taken together form a double bond

between positions 9 and 11, R_4 and R_6 are hydrogen, R_{12} and R_{14} taken together form a double bond between positions 4 and 5, R_5 is α-F, R_9 is β-CH_3, R_{10} is α-OH, R_{13} and R_{15} are =O and R_{23} is -OP(O)-$(OH)_2$.

R_{24} = C, C_1-C_2 double bond, O;

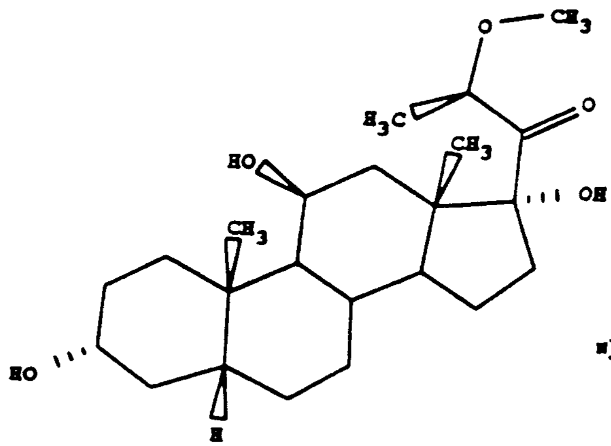
R_{25} = $C(R_{15})CH_2$-R_{23}, OH, OR_{26}, $OC(=O)R_{27}$, R_{26}, COOH, $C(=O)OR_{26}$, $CHOHCH_2OH$, $CHOHCH_2OR_{26}$, $CHOHCH_2OC(=O)R_{27}$, CH_2CH_2OH, $CH_2CH_2OR_{26}$, $CH_2CH_2OC(=O)R_{27}$, CH_2CN, CH_2N_3, CH_2NH_2, CH_2NHR_{26}, $CH_2N(R_{26})_2$, CH_2OH, CH_2OR_{26}, $CH_2O(C=O)R_{27}$, $CH_2O(P=O)(OH)_2$, $CH_2O(P=O)(OR_{26})_2$, CH_2SH, CH_2S-R_{26}, $CH_2SC(=O)R_{27}$, $CH_2NC(=O)R_{27}$, $C(=O)CHR_{28}OH$, $C(=O)CHR_{28}OR_{26}$, $C(=O)CHR_{28}OC(=O)R_{27}$ or R_{10} and R_{25} taken together may be $=C(R_{28})_2$, that is, an optionally alkyl substituted methylene group;

wherein R_{26} = C_1-C_6 (alkyl, branched alkyl, cycloalkyl, haloalkyl, aralkyl, aryl);

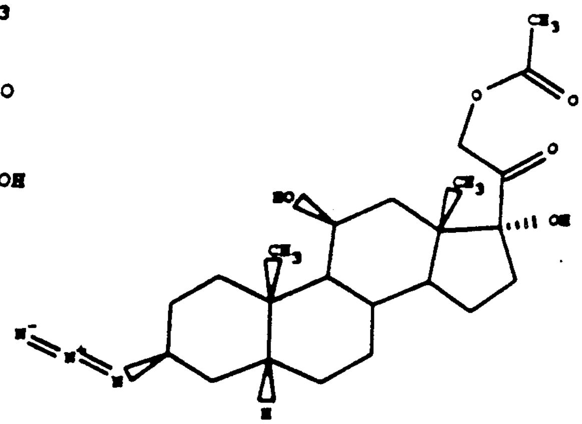
R_{27} = R_{26} + OR_{26}; R_{28} = H, C_1-C_6 (alkyl, branched alkyl, cycloalkyl).

Unless specified otherwise, all substituent groups attached to the cyclopentanophenanthrene moiety of Structures [A] and [B] may be in either the alpha or beta position. Additionally, the above structures include all pharmaceutically acceptable salts of the angiostatic steroids.

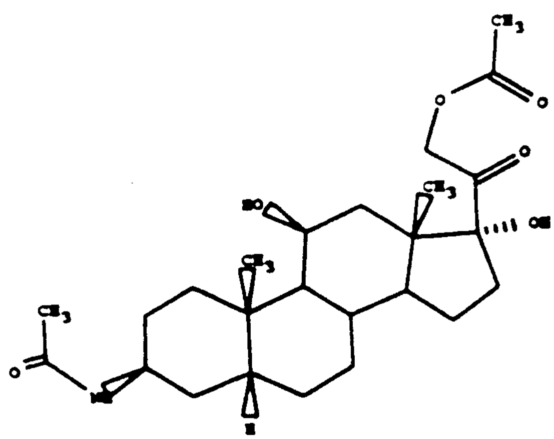
Preferred angiostatic steroids are:



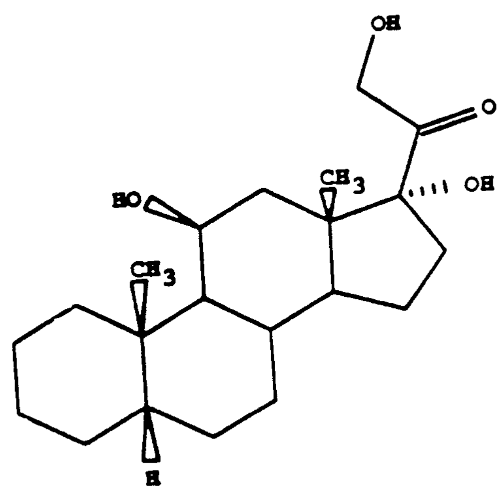
21-METHYL-5β-PREGNAN-3α,11β,17α,
21-TETROL-20-ONE 21-METHYL ETHER



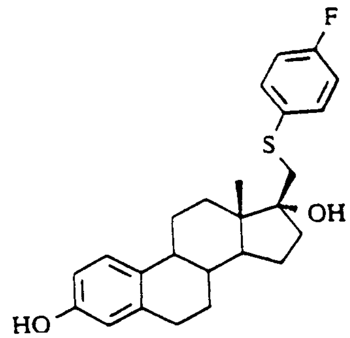
3β-AZIDO-5β-PREGNAN-11β,
17α,21-TRIOL-20-ONE-21-ACETATE



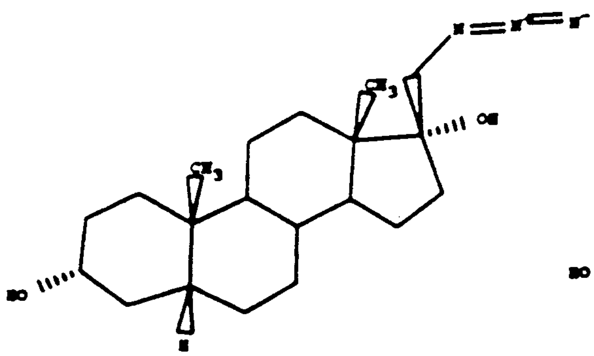
3β-ACETAMIDO-5β-PREGNAN-
11β,17α,21-TRIOL-20-ONE
21-ACETATE



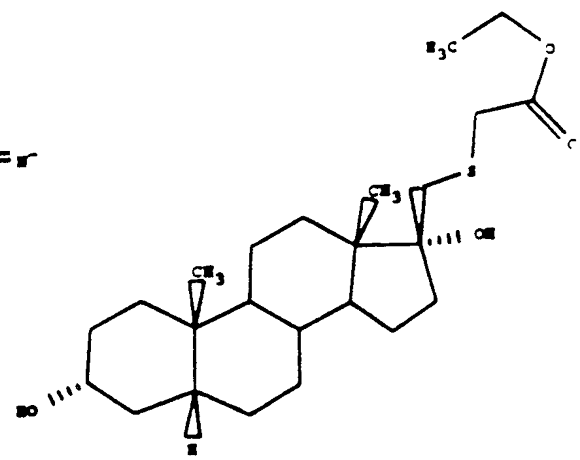
5β-PREGNAN-11β,17α,21-TRIOL-20-ONE



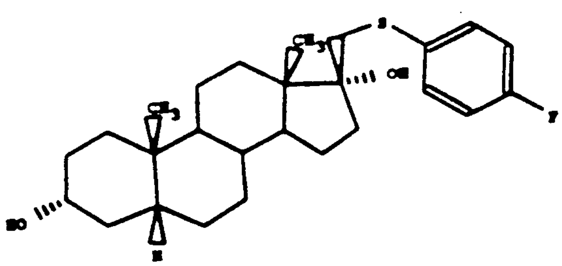
17-((4-FLUORO)THIOPHENOXY)METHYL-1,3,5-ESTRATRIEN-3,17-DIOL



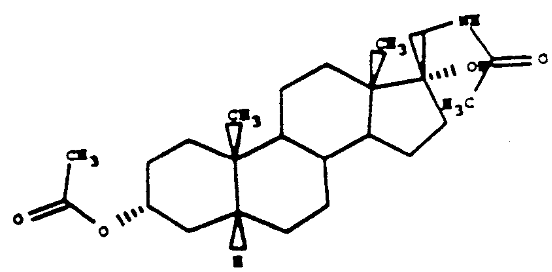
20-AZIDO-21-NOR-5β-PREGNAN-3α, 17α-DIOL



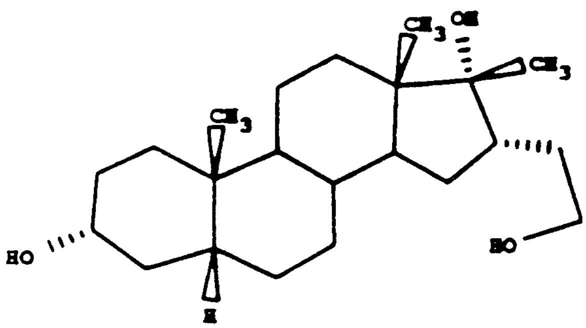
20-(CARBETHOXYMETHYL)THIO-21-NOR-5β-PREGNAN-3α, 17α-DIOL



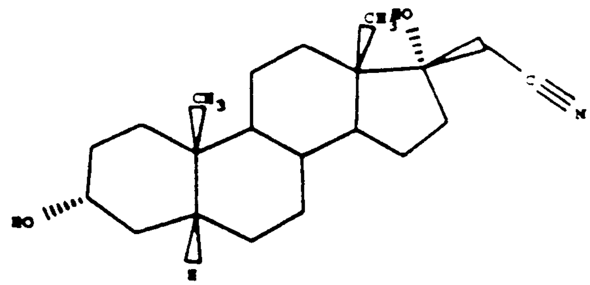
20-(4-FLUOROPHENYL)THIO-21-NOR-PREGNAN-3α,17α-DIOL



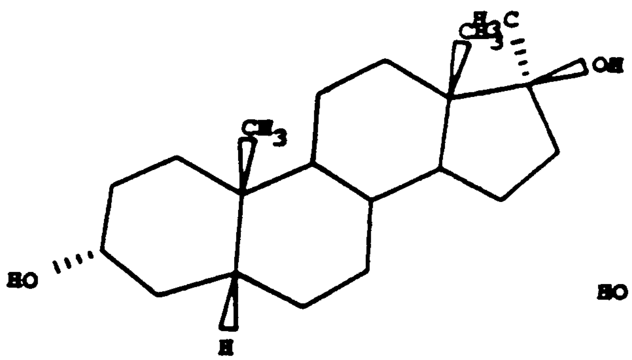
20-ACETAMIDO-21-NOR-5β–PREGNAN-3α–5β–17α-DIOL-3-ACETATE



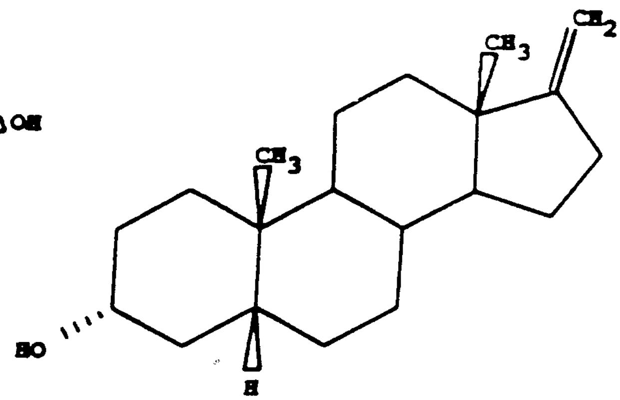
16α-(2-HYDROXYETHYL)-17β-METHYL-5β-ANDROSTAN-3α,17α-DIOL



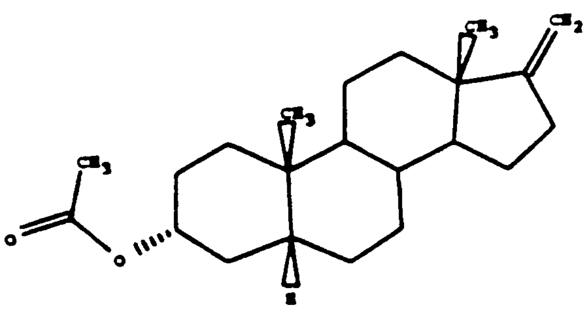
20-CYANO-21-NOR--5β-PREGNAN-3α,17α-DIOL



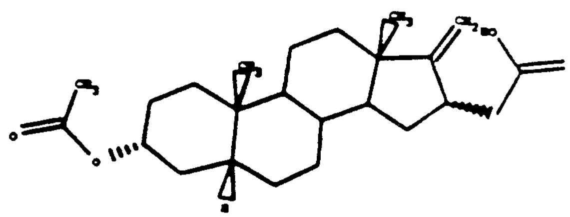
17α-METHYL-5β-ANDROSTAN-3α,17β-DIOL



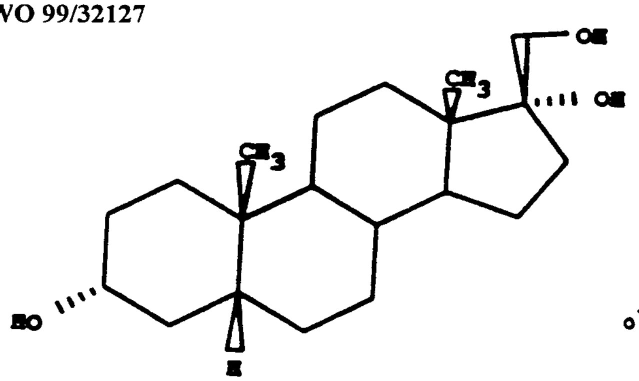
21-NOR-5β-PREGN-17(20)-EN-3α-OL



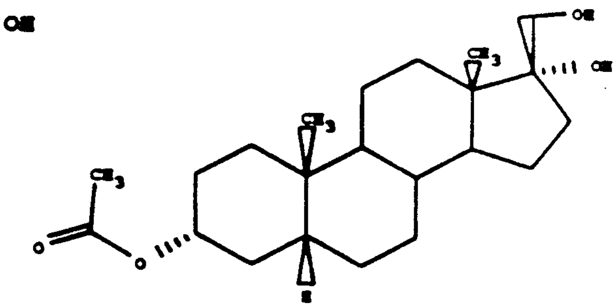
21-NOR-5β-PREGN-17(20)-EN-3α-OL-3-ACETATE



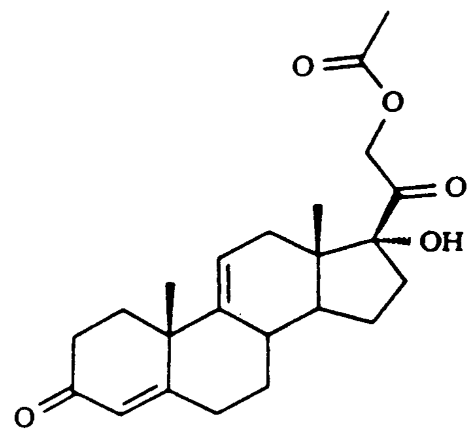
21-NOR-5β-PREGN-17(20)-EN-3α-OL-16-ACETIC ACID-3-ACETATE



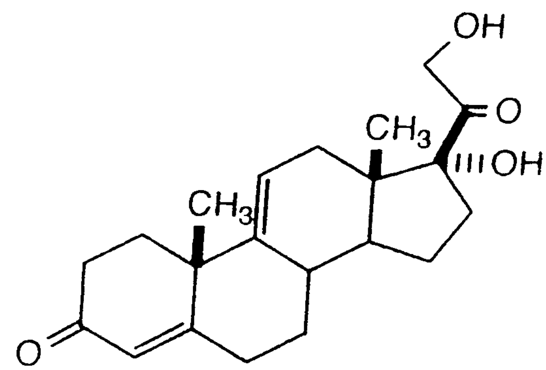
21-NOR-5β-PREGNAN-3α,17α,20-TRIOL



21-NOR-5β-PREGNAN-3α,17α,20-TRIOL-3-ACETATE



4,9(11)-PREGNADIEN-17∝,21-DIOL-3,20-DIONE-21-ACETATE



4,9(11)-PREGNADIEN-17∝,21-DIOL-3,20-DIONE

The more preferred compounds are 21-methyl-5β-pregnan-3∝, 11β, 17∝,21-tetrol 20-one-21-methyl ether; 3β-azido-21-acetoxy-5β-pregnan-11β, 17∝-diol-20-one; 3β-acetamido-21-acetoxy-5β-pregnan-11β, 17∝-diol-20-one; and 5β-pregnan-11β, 17∝, 21-triol-20-one. The most preferred compounds are 4,9(11)-pregnadien-17∝,21-diol-3,20-dione-21-acetate and 4,9(11)-pregnadien-17∝,21-diol-3,20-dione.

The angiostatic steroids of the present invention may be incorporated in various formulations for delivery to the eye. For example, topical formulations can be used and can include ophthalmologically acceptable preservatives, surfactants, viscosity enhancers, buffers, sodium chloride and water to form aqueous sterile ophthalmic solutions and suspensions. In order to prepare sterile ophthalmic ointment formulations, an angiostatic steroid is combined with a preservative in an appropriate vehicle, such as mineral oil, liquid lanolin or white petrolatum.

Sterile ophthalmic gel formulations comprising the angiostatic steroids of the present invention can be prepared by suspending an angiostatic steroid in a hydrophilic base prepared from a combination of, for example, Carbopol-940 (a carboxyvinyl polymer available from the B.F. Goodrich Company) according to published formulations for analogous ophthalmic preparations. Preservatives and tonicity agents may also be incorporated in such gel formulations.

The specific type of formulations selected will depend on various factors, such as the angiostatic steroid or its salt being used, and the dosage frequency. Topical ophthalmic aqueous solutions, suspensions, ointments and gels are the preferred dosage forms. The angiostatic steroid will normally be contained in these formulations in an amount of from about 0.005 to about 5.0 weight percent (wt.%). Preferable concentrations range from about 0.05 to about 2.0 wt.%. Thus, for topical administration, these formulations are delivered to the surface of the eye one to four times per day, depending upon the routine discretion of the skilled clinician.

The following examples illustrate formulations and synthesis of compounds of the present invention, but are in no way limiting.

Example 1

Component	wt.%
Angiostatic Steroid	0.005-5.0
Tyloxapol	0.01-0.05
HPMC	0.5
Benzalkonium Chloride	0.01
Sodium Chloride	0.8
Edetate Disodium	0.01
NaOH/HCl	q.s. pH 7.4
Purified Water	q.s. 100 mL

Example 2

Component	wt.%
4,9(11)-pregnadien-17α,21-diol-3,20-dione-21-acetate	1.0
Mannitol	2.40
Carbopol 974P	0.50
Polysorbate 80	0.05
Benzalkonium Chloride	0.01
Sodium Chloride	0.4
Edetate Disodium	0.01
NaOH/HCl	q.s. pH 7.4
Purified Water	q.s. 100 mL

Example 3

Preparation of 5β-Pregnan-11β, 17∝, 21-triol-20-one

Tetrahydrocortisol-F-21-t-butyldiphenylsilyl ether (PS03842)

A solution of 4.75 g (17.3 mmol) of t-butyldiphenylchlorosilane in 5 mL of dry DMF was added dropwise to a stirred solution of 5.7 g (15.6 mmol) of tetrahydrocortisol-F (Steraloids No. P9050) and 2.3 g (19 mmol) of 4-dimethylaminopyridine (DMAP) in 30 mL of dry DMF, under N_2, at -25 to -30°C (maintained with CO_2 - MeCN). After a further 20 min at -30°C, the mixture was allowed to warm to 23°C overnight.

The mixture was partitioned between ether and water, and the organic solution was washed with brine, dried ($MgSO_4$), filtered and concentrated to give 10.7 g of a white foam.

This material was purified by flash column chromatography (400 g silica; 62.5 to 70% ether/hexane). The 3-siloxy isomer eluted first, followed by mixed fractions, followed by the title compound. The concentrated mixed fractions (4.0 g) were chromatographed on the same column with 35% ethyl acetate/hexane. The total yield of the 3-siloxy isomer was 0.42 g (5%), and of the title compound, 5.05 g (53.5%). Continued elution with 25% MeOH/EtOAc allowed recovery of unreacted tetrahydrocortisol-F.

PSO3842

NMR (200 MHz ^1H) ($CDC1_3$): δ0.63 (s, 3H, Me-18); 1.11 (s, 9H, t-Bu); 1.12 (s, 3H, Me-19); 2.57 (t, J=13, 1H, H-8); 2.6 (s, 1H, OH-17); 3.63 (sept, J=2.5, 1H, H-3); 4.15 (br s, 1H, H-11); 4.37 and 4.75 (AB, J=20, 2H, H-21); 7.4 (m, 6H) and 7.7 (m, 4H) (Ph_2).
NMR (200 MHz ^1H) (DMSO-d_6): δ0.64 (s, 3H, Me-18); 1.02 (s, 9H, t-Bu); 1.07 (s, 3H, Me-19); 2.50 (t, J=13, 1H, H-8); 3.37 (m, 1H, H-3); 3.94 (d, J=2, 1H, OH-11); 4.00 (br s, 1H, H-11); 4.42 (d, J=5, 1H, OH-3); 4.38 and 4.83 (AB, J=20, 2H, H-21); 5.11 (s, 1H, OH-17); 7.45 (m, 6H) and 7.6 (m, 4H) (Ph_2).
NMR (50.3 - MHz ^{13}C) ($CDCl_3$): <u>17.4</u> (C-18); 19.3 (C-16); 23.7 (C-15); 26.3 (C-7); <u>26.6</u> (C-19); <u>26.8</u> (<u>Me</u>$_3$C); 27.2 (C-6); 30.9 (C-2); <u>31.5</u> (C-8); 34.1 (Me$_3$<u>C</u>); 34.8 (C-10); 35.2 (C-1); 36.2 (C-4);

39.7 (C-13); 43.5 (C-5); 44.3 (C-9); 47.4 (C-12); 52.1 (C-14); 67.8 (C-11); 68.9 (C-21); 71.7 (C-3); 89.8 (C-14); 127.8, 129.8, 132.8, 132.9, 135.7, 135.8 (diastereotopic Ph_2); 208.8 (C-20). Underlined resonances showed inversion in the APT experiment. Assignments: E. Breitmaier, W. Voelter "Carbon-13 NMR Spectroscopy," 3d ed., VCH, 1987; pp. 345-348.

IR (KBr) 3460, 2930, 2860, 1720, 1428, 1136, 1113, 1070, 1039, 703 cm^{-1}.

This compound did not show a sharp melting point but turned to a foam at 80-100°C. Numerous attempts at recrystallization failed.

5β-Pregnan-11β, 17∝, 21-triol-20-one

A solution of PSO3842 (0.91 g, 1.50 mmol) and thiocarbonyl diimidazole (1.05 g, 5.9 mmol) in 8 mL of anhydrous dioxane was refluxed under N_2 for 3.5 h. The cooled solution was partitioned between ether and water and the organic solution was washed with brine, dried ($MgSO_4$), filtered and concentrated. The residue was chromatographed (120 g SiO_2, 35% EtOAc/hexane) giving 0.86 g (80%) of the imidazolyl thioester.

A solution of 0.75 g (1.05 mmol) of this compound in 100 mL of anhydrous dioxane was added dropwise over 2.2 h to a rapidly stirred, refluxing solution of 1.6 mL (5.9 mmol) of Bu_3SnH in 100 mL of anhydrous dioxane under N_2. After a further 1 h at reflux, the solution was cooled, concentrated and the residue chromatographed (200 g SiO_2, 9% EtOAc/hexane) giving 0.43 g (70%) of the 3-deoxy-21-silyl ether. This material was dissolved in 20 mL of methanol; $Bu_4NF{\cdot}3H_20$ (0.50 g, 1.6 mmol) was added, and the mixture was heated to reflux under N_2 for 4 h. The cooled solution was diluted with 2 volumes of EtOAc, concentrated to 1/4 volume, partitioned ($EtOAc/H_2O$), and the organic solution was washed with brine, dried ($MgSO_4$), filtered and concentrated. The residue (0.40 g) was chromatographed (30 g SiO_2, 40% EtOAc/hexane) to give 0.25 g (98%) of an oil.

This oil was crystallized (n-BuCl) to afford 0.14 g of the title compound as a white solid, m.p. 167-170°C.

IR (KBr): 3413 (br), 2934, 1714, 1455, 1389, 1095, 1035 cm^{-1}.

MS (CI): 351 (M +1).

NMR (200 MHz ^1H, DMSO-d_6): δ0.69 (s, 3H, Me-18); 1.14 (s, 3H, Me-19); 0.8-2.0 (m); 2.5 (t, J=13, 1H, H-8); 3.96 (d, J=2, 1H, OH-11); 4.1 (br s, 1H, H-11); 4.1 and 4.5 (AB, further split by 5 Hz, 2H, H-21); 4.6 (t, J=5, 1H, OH-21); 5.14 (s, 1H, OH-17).

Anal. Calc'd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78.
Found: C, 71.69; H, 9.66.

Example 4

Preparation of 21-Methyl-5β-pregnan-3α, 11β, 17α, 21-tetrol-20-one 21-methyl ether

Sodium hydride (60% oil dispersion, 0.10 g, 2.5 mmol) was added to a stirred solution of tetrahydrocortisol-F (0.73 g, 2.0 mmol) and CH_3I (0.60 mL, 9.6 mmol) in 8 mL of anhydrous DMF under N_2. Hydrogen was evolved, and the temperature rose to 35°C. After 1 h, the mixture was diluted with EtOAc, extracted with water (until neutral) and brine, dried ($MgSO_4$), filtered and concentrated. The residue was chromatographed (70 g SiO_2, 80% EtOAc/hexane) to give 0.17 g of a white solid, MS (CI) = 395 (M +1). This material was recrystallized (EtOAc-n-BuCl) to afford 0.12 g (16%) of the title compound as a feathery white solid, m.p. 208-213 °C.

IR (KBr): 3530, 3452, 2939, 2868, 1696 (s, CO), 1456, 1366, 1049 cm^{-1}.

NMR (200 MHz ^{1}H, DMSO-d_6): δ0.74 (s, 3H, Me-18); 1.09 (s, 3H, Me-19); 1.14 (d, J=6.6, 3H, C-21 Me); 0.8-2.0 (m); 2.47 (t, J=13, 1H, H-8); 3.18 (s, 3H, OMe); 3.35 (m, 1H, H-3); 4.00 (d, J=2, 1H, OH-11); 4.07 (br s, 1H, H-11); 4.37 (q, J=6.6, 1H, H-21); 4.43 (d, J=5, 1H, OH-3); 5.16 (s, 1H, OH-17).

Anal. Calc'd for $C_{23}H_{38}O_5$: C, 70.01; H, 9.71.
Found: C, 70.06; H, 9.76.

Example 5

Preparation of 3β-Azido-21-acetoxy-5β-pregnan-11β, 17α-diol-20-one

A solution of triphenylphosphine (2.6 g, 10 mmol) in 10 mL of toluene was carefully added to a stirred solution of PS03842 (see Example 4) (1.75 g, 2.90 mmol), diphenylphosphoryl azide (2.2 mL, 10.2 mmol) and diethyl azodicarboxylate (1.55 mL, 10 mmol) under N_2, keeping the internal temperature below 35°C (exothermic). The solution was stirred for 1.2 h, then diluted with ether, washed with water and brine, dried ($MgSO_4$), filtered and concentrated and the residue (9.5 g, oil) chromatographed 175 g SiO_2, 15% EtOAc/hexane) giving 1.83 g of a viscous oil.

A solution of 1.73 g of this material and 1.75 g (5.5 mmol) of $Bu_4NF{\cdot}3H_2O$ in 20 mL of methanol was refluxed under N_2 for 2.5 h. The crude product (1.94 g) was isolated with ethyl acetate and chromatographed (100 g SiO_2, 50% EtOAc/hexane) giving 0.60 g (56%) of a white semisolid. Trituration (4:1 hexane-ether) gave 0.57 g (53%) of a solid.

A stirred solution of 0.40 g of this material in 3 mL of dry pyridine was treated with 0.3 mL of acetic anhydride and stirred overnight at 23°C under N_2. The mixture was quenched with 1 mL of methanol, stirred for 15 min, diluted with ether, washed with 1 M aqueous HCl, water (until neutral), brine, dried (MgSO4), filtered and concentrated. The residue (0.41 g, oil) was chromatographed (35 g SiO_2, 33% EtOAc/hexane) to afford 0.33 g (76%) of the title compound as a white foam, m.p. 80-90°C (dec).

IR (KBr): 3505, 2927, 2866, 2103 (vs), 1721 (sh 1730), 1268, 1235 cm^{-1}.

NMR (200 MHz ^1H, $CDCl_3$): δ0.92 (s, 3H, Me-18); 1.21 (s, 3H, Me-19); 1.0-2.1 (m); 2.17 (s, 3H, Ac); 2.25 (s 1H, OH-17); 2.74 (m, 1H, H-8); 3.97 (br s, 1H, H-3); 4.31 (br s, 1H, H-11); 4.94 (AB, J=17, Δν=60, 2H, H-21).

Anal. Calc'd for $C_{23}H_{35}N_3O_5$: C, 63.72; H, 8.14; N, 9.69.
Found: C, 63.39; H, 8.18; N, 9.45.

Example 6

Preparation of 3β-Acetamido-21-acetoxy-5β-pregnan-11β, 17α-diol-20-one

A solution of 3β-azido-21-acetoxy-5β-pregnan-11β,17α-diol-20-one (0.15 g, 0.35 mmol) in 8 mL of absolute ethanol containing 0.03 g of 10% Pd on C was stirred under H_2 (1 atm) at 23°C for 2 h. The mixture was filtered and concentrated, the residue dissolved in EtOAc, the basic material extracted into 1 M aqueous HCl, liberated (Na_2CO_3), extracted (EtOAc) and the organic extract washed with water (until neutral) and brine, dried ($MgSO_4$), filtered and concentrated to provide 58 mg of a solid.

This material was acetylated (1.0 mL of dry pyridine, 0.20 mL of Ac_2O, 23°C, N_2, overnight), followed by workup (as described for the steroid of Example 6 [last step]) affording a crude product that was chromatographed (25 g SiO_2, EtOAc). This product was triturated with ether to afford 51 mg (33%) of product as a white solid, m.p. 179-181°C.

Ms (CI, isobutane): (M +1) = 450 (M^+), 432, 391, 371, 348.

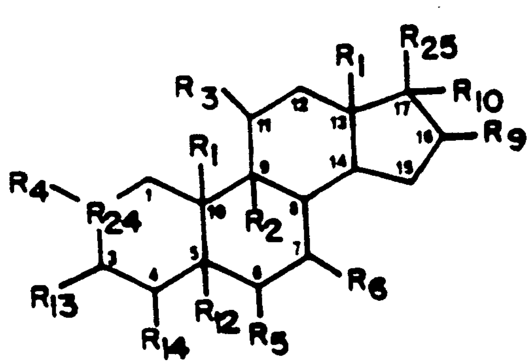
IR (KBr): 3398 (br), 2932, 2865, 1720 (sh. 1740), 1652, 1538, 1375, 1265, 1236 cm^{-1}.

NMR (200 MHz ^1H, $CDCl_3$): δ0.89, 1.22, 1.99, 2.17 (all s, 3H); 1.0-2.2 (m); 2.7 (t, J=13, 1H, H-8); 3.03 (s, 1H, OH-17); 4.2 (br s, 1H, H-11); 4.3 (br s, 1H, H-3); 4.96 (AB, J=17.5, Δν=42, 2H, H-21); 5.8 (d, J=10, 1H, NH).

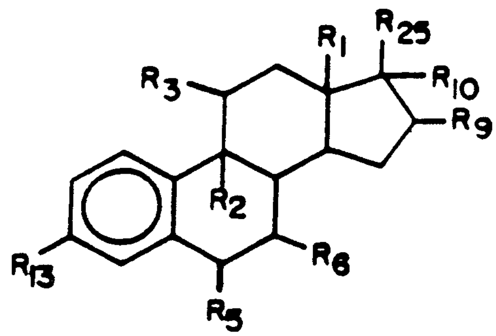
We Claim:

1. A method for treating GLC1A glaucoma which comprises by administering a pharmaceutically effective amount of an angiostatic agent.

2. The method of Claim 1 wherein the angiostatic agent has the following structure:



Structure [A]



Structure [B]

wherein R_1 is H, β-CH_3 or β-C_2H_5;

R_2 is F, C_9-C_{11} double bond, C_9-C_{11} epoxy, H or Cl;

R_3 is H, OR_{26}, $OC(=O)R_{27}$, halogen, C_9-C_{11} double bond, C_9-C_{11} epoxy, =O, -OH, -O-alkyl(C_1-C_{12}), -OC(=O)alkyl(C_1-C_{12}), -OC(=O)ARYL, -OC(=O)N(R)$_2$ or -OC(=O)OR_7, wherein ARYL is furyl, thienyl, pyrrolyl, or pyridyl and each of said moieties is optionally substituted with one or two (C_1-C_4)alkyl groups, or ARYL is -$(CH_2)_f$-phenyl wherein f is 0 to 2 and the phenyl ring is optionally substituted with 1 to 3 groups selected from chlorine, fluorine, bromine, alkyl(C_1-C_3), alkoxy(C_1-C_3), thioalkoxy-(C_1-C_3), Cl_3C-, F_3C-, -NH_2 and -$NHCOCH_3$ and R is hydrogen, alkyl (C_1-C_4), or phenyl and each R can be the same or different, and R_7 is ARYL as herein defined, or alkyl(C_1-C_{12});

R_4 is H, CH_3, Cl or F;

R_5 is H, OH, F, Cl, Br, CH_3, phenyl, vinyl or allyl;

R_6 is H or CH_3;

R_9 is $CH_2CH_2OR_{26}$, $CH_2CH_2OC(=O)R_{27}$, H, OH, CH_3, F, $=CH_2$, $CH_2C(=O)OR_{28}$,, OR_{26}, $O(C=O)R_{27}$ or $O(C=O)CH_2(C=O)OR_{26}$

R_{10} is $-C\equiv CH$, $-CH=CH_2$, halogen, CN, N_3, OR_{26}, $OC(=O)R_{27}$, H, OH, CH_3 or R_{10} forms a second bond between positions C-16 and C-17;

R_{12} is H or forms a double bond with R_1 or R_{14};

R_{13} is halogen, OR_{26}, $OC(=O)R_{27}$, NH_2, NHR_{26}, $NHC(=O)R_{27}$, $N(R_{26})_2$, $NC(=O)R_{27}$, N_3, H, -OH, =O, $-O-P(=O)(OH)_2$, or $-O-C(=O)-(CH_2)_tCOOH$ where t is an integer from 2 to 6;

R_{14} is H or forms a double bond with R_{12};

R_{15} is H, =O or -OH;

and R_{23} with R_{10} forms a cyclic phosphate;

wherein R_9 and R_{15} have the meaning defined above;

or wherein R_{23} is -OH, $O-C(=O)-R_{11}$, $-OP(O)-(OH)_2$, or $-O-C(=O)-(CH_2)_tCOOH$ wherein t is an integer from 2 to 6; and R_{11} is $-Y-(CH_2)_n-X-(CH_2)_m-SO_3H$, $-Y'-(CH_2)_p-X'-(CH_2)_q-NR_{16}R_{17}$ or $-Z(CH_2)_rQ$,

wherein Y is a bond or -O-; Y' is a bond, -O-, or -S-; each of X and X' is a bond,$-CON(R_{18})-$, $-N(R_{18})CO-$, -O-, -S-, -S(O)-, or $-S(O_2)-$; R_{18} is hydrogen or alkyl (C_1-C_4); each of R_{16} and R_{17} is a lower alkyl group of from 1 to 4 carbon atoms optionally substituted with one hydroxyl or R_{16} and R_{17} taken together with the nitrogen atom to which each is attached forms a monocyclic heterocycle selected from pyrrolidino, piperidino, morpholino, thiomorpholino, piperazino or N(lower)alkyl-piperazino wherein alkyl has from 1 to 4 carbon atoms; n is an integer of from 4 to 9; m is an integer of from 1 to 5; p is an integer of from 2 to 9; q is an integer of from 1 to 5;

Z is a bond or -O-; r is an integer of from 2 to 9; and Q is one of the following:

(1) $-R_{19}-CH_2COOH$ wherein R_{19} is -S-, -S(O)-, $-S(O)_2-$, $-SO_2N(R_{20})-$, or $N(R_{20})SO_2-$; and R_{20} is hydrogen or lower alkyl-(C_1-C_4); with the proviso that the total number of carbon atoms in R_{20} and $(CH_2)_r$ is not greater than 10; or

(2) -CO-COOH; or

(3) $CON(R_{21})CH(R_{22})COOH$ wherein R_{21} is H and R_{22} is H, CH_3, $-CH_2COOH$, $-CH_2CH_2COOH$, $-CH_2OH$, $-CH_2SH$, $-CH_2CH_2SCH_3$, or $-CH_2Ph-OH$ wherein Ph-OH is p-hydroxyphenyl;

or R_{21} is CH_3 and R_{22} is H;

or R_{21} and R_{22} taken together are $-CH_2CH_2CH_2-$;

or $-N(R_{21})CH(R_{22})COOH$ taken together is $-NHCH_2CONHCH_2COOH$; and pharmaceutically acceptable salts thereof;

with the proviso that if R_{23} is a phosphate, it must form a cyclic phosphate, with R_{10} when R_{13} is =O, except for the compound wherein R_1 is β-CH_3, R_2 and R_3 taken together form a double bond between positions 9 and 11, R_4 and R_6 are hydrogen, R_{12} and R_{14} taken together form a double bond between positions 4 and 5, R_5 is ∝-F, R_9 is β-CH_3, R_{10} is ∝-OH, R_{13} and R_{15} are =O and R_{23} is $-OP(O)-(OH)_2$.

R_{24} = C, C_1-C_2 double bond, O;

R_{25} = $C(R_{15})CH_2-R_{23}$, OH, OR_{26}, $OC(=O)R_{27}$, R_{26}, COOH, $C(=O)OR_{26}$, $CHOHCH_2OH$, $CHOHCH_2OR_{26}$, $CHOHCH_2OC(=O)R_{27}$, CH_2CH_2OH, $CH_2CH_2OR_{26}$, $CH_2CH_2OC(=O)R_{27}$, CH_2CN, CH_2N_3, CH_2NH_2, CH_2NHR_{26}, $CH_2N(R_{26})_2$, CH_2OH, CH_2OR_{26}, $CH_2O(C=O)R_{27}$, $CH_2O(P=O)(OH)_2$, $CH_2O(P=O)(OR_{26})_2$, CH_2SH, CH_2S-R_{26}, $CH_2SC(=O)R_{27}$, $CH_2NC(=O)R_{27}$, $C(=O)CHR_{28}OH$, $C(=O)CHR_{28}OR_{26}$, $C(=O)CHR_{28}OC(=O)R_{27}$ or R_{10} and R_{25} taken together may be $=C(R_{28})_2$, that is, an optionally alkyl substituted methylene group;

wherein R_{26} = C_1-C_6 (alkyl, branched alkyl, cycloalkyl, haloalkyl, aralkyl, aryl);

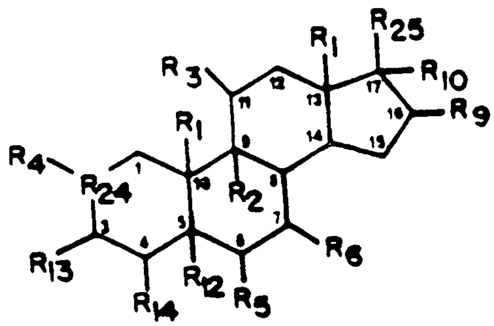
R_{27} = R_{26} + OR_{26}; R_{28} = H, C_1-C_6 (alkyl, branched alkyl, cycloalkyl).

3. The method of Claim 2 wherein the compound is selected from the group consisting of 21-methyl-5β-pregnan-3∝,11β, 17∝, 21-tetrol-20-one 21-methyl ether; 3β-azido-21-acetoxy-5β-pregnan-11β, 17∝-diol-20-one; 3β-acetamido-21-acetoxy-5β-pregnan-11β, 17∝-diol-20-one; 5β-pregnan-11β, 17∝, 21-triol-20-one; 4, 9(11)-pregnadien-17∝,21-diol-3,20-dione-21-acetate and 4, 9(11)-pregnadien-17∝,21-diol-3,20-dione.

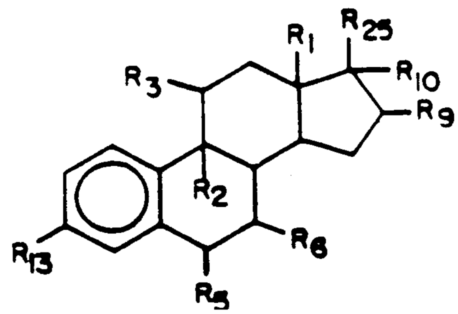
4. The method of Claim 3 wherein the compound is selected from the group consisting of 4, 9(11)-pregnadien-17∝,21-diol-3,20-dione-21-acetate and 4, 9(11)-pregnadien-17∝,21-diol-3,20-dione.

5. A composition for controlling GLC1A glaucoma comprising a pharmaceutically effective amount of an angiostatic agent.

6. The composition of Claim 5 wherein the angiostatic steroid has the following structure:



Structure [A]



Structure [B]

wherein R_1 is H, β-CH_3 or β-C_2H_5;

R_2 is F, C_9-C_{11} double bond, C_9-C_{11} epoxy, H or Cl;

R_3 is H, OR_{26}, $OC(=O)R_{27}$, halogen, C_9-C_{11} double bond, C_9-C_{11} epoxy, =O, -OH, -O-alkyl(C_1-C_{12}), -OC(=O)alkyl(C_1-C_{12}), -OC(=O)ARYL, -OC(=O)N(R)$_2$ or -OC(=O)OR_7, wherein ARYL is furyl, thienyl, pyrrolyl, or pyridyl and each of said moieties is optionally substituted with one or two (C_1-C_4)alkyl groups, or ARYL is -$(CH_2)_f$-phenyl wherein f is 0 to 2 and the phenyl ring is optionally substituted with 1 to 3 groups selected from chlorine, fluorine, bromine, alkyl(C_1-C_3), alkoxy(C_1-C_3), thioalkoxy-(C_1-C_3), Cl_3C-, F_3C-, -NH_2 and -$NHCOCH_3$ and R is hydrogen, alkyl (C_1-C_4), or phenyl and each R can be the same or different, and R_7 is ARYL as herein defined, or alkyl(C_1-C_{12});

R_4 is H, CH_3, Cl or F;

R_5 is H, OH, F, Cl, Br, CH_3, phenyl, vinyl or allyl;

R_6 is H or CH_3;

R_9 is $CH_2CH_2OR_{26}$, $CH_2CH_2OC(=O)R_{27}$, H, OH, CH_3, F, =CH_2, $CH_2C(=O)OR_{28}$,, OR_{26}, $O(C=O)R_{27}$ or $O(C=O)CH_2(C=O)OR_{26}$

R_{10} is -C≡CH, -CH=CH_2, halogen, CN, N_3, OR_{26}, $OC(=O)R_{27}$, H, OH, CH_3 or R_{10} forms a second bond between positions C-16 and C-17;

R_{12} is H or forms a double bond with R_1 or R_{14};

R_{13} is halogen, OR_{26}, $OC(=O)R_{27}$, NH_2, NHR_{26}, $NHC(=O)R_{27}$, $N(R_{26})_2$, $NC(=O)R_{27}$, N_3, H, -OH, =O, -O-P(=O)$(OH)_2$, or -O-C(=O)-$(CH_2)_t$COOH where t is an integer from 2 to 6;

R_{14} is H or forms a double bond with R_{12};

R_{15} is H, =O or -OH;

and R_{23} with R_{10} forms a cyclic phosphate;

wherein R_9 and R_{15} have the meaning defined above;

or wherein R_{23} is -OH, O-C(=O)-R_{11}, -OP(O)-$(OH)_2$, or -O-C(=O)-$(CH_2)_t$COOH wherein t is an integer from 2 to 6; and R_{11} is -Y-$(CH_2)_n$-X-$(CH_2)_m$-SO_3H,

-Y'-$(CH_2)_p$-X'-$(CH_2)_q$-$NR_{16}R_{17}$ or -Z$(CH_2)_r$Q,

wherein Y is a bond or -O-; Y' is a bond, -O-, or -S-; each of X and X' is a bond,-CON(R_{18})-, -N(R_{18})CO-, -O-, -S-, -S(O)-, or -S(O_2)-; R_{18} is hydrogen or alkyl (C_1-C_4); each of R_{16} and R_{17} is a lower alkyl group of from 1 to 4 carbon atoms optionally substituted with one hydroxyl or R_{16} and R_{17} taken together with the nitrogen atom to which each is attached forms a monocyclic heterocycle selected from pyrrolidino, piperidino, morpholino, thiomorpholino, piperazino or N(lower)alkyl-piperazino wherein alkyl has from 1 to 4 carbon atoms; n is an integer of from 4 to 9; m is an integer of from 1 to 5; p is an integer of from 2 to 9; q is an integer of from 1 to 5;

Z is a bond or -O-; r is an integer of from 2 to 9; and Q is one of the following:

(1) -R_{19}-CH_2COOH wherein R_{19} is -S-, -S(O)-, -S$(O)_2$-, -SO_2N(R_{20})-, or N(R_{20})SO_2-; and R_{20} is hydrogen or lower alkyl-(C_1-C_4); with the proviso that the total number of carbon atoms in R_{20} and $(CH_2)_r$ is not greater than 10; or

(2) -CO-COOH; or

(3) CON(R_{21})CH(R_{22})COOH wherein R_{21} is H and R_{22} is H, CH_3, -CH_2COOH, -CH_2CH_2COOH, -CH_2OH, -CH_2SH, -$CH_2CH_2SCH_3$, or

-CH_2Ph-OH wherein Ph-OH is p-hydroxyphenyl;

or R_{21} is CH_3 and R_{22} is H;

or R_{21} and R_{22} taken together are -$CH_2CH_2CH_2$-;

or -N(R_{21})CH(R_{22})COOH taken together is -NHCH_2CONHCH_2COOH; and pharmaceutically acceptable salts thereof;

with the proviso that if R_{23} is a phosphate, it must form a cyclic phosphate, with R_{10} when R_{13} is = O, except for the compound wherein R_1 is β-CH_3, R_2 and R_3 taken together form a double bond between positions 9 and 11, R_4 and R_6 are hydrogen, R_{12} and R_{14} taken together form a double bond between positions 4 and 5, R_5 is ∝-F, R_9 is β-CH_3, R_{10} is ∝-OH, R_{13} and R_{15} are =O and R_{23} is -OP(O)-$(OH)_2$.

R_{24} = C, C_1-C_2 double bond, O;

R_{25} = $C(R_{15})CH_2$-R_{23}, OH, OR_{26}, $OC(=O)R_{27}$, R_{26}, COOH, $C(=O)OR_{26}$, $CHOHCH_2OH$, $CHOHCH_2OR_{26}$, $CHOHCH_2OC(=O)R_{27}$, CH_2CH_2OH, $CH_2CH_2OR_{26}$, $CH_2CH_2OC(=O)R_{27}$, CH_2CN, CH_2N_3, CH_2NH_2, CH_2NHR_{26}, $CH_2N(R_{26})_2$, CH_2OH, CH_2OR_{26}, $CH_2O(C=O)R_{27}$, $CH_2O(P=O)(OH)_2$, $CH_2O(P=O)(OR_{26})_2$, CH_2SH, CH_2S-R_{26}, $CH_2SC(=O)R_{27}$, $CH_2NC(=O)R_{27}$, $C(=O)CHR_{28}OH$, $C(=O)CHR_{28}OR_{26}$, $C(=O)CHR_{28}OC(=O)R_{27}$ or R_{10} and R_{25} taken together may be $=C(R_{28})_2$, that is, an optionally alkyl substituted methylene group;

wherein R_{26} = C_1-C_6 (alkyl, branched alkyl, cycloalkyl, haloalkyl, aralkyl, aryl);

R_{27} = R_{26} + OR_{26}; R_{28} = H, C_1-C_6 (alkyl, branched alkyl, cycloalkyl).

7. The composition of Claim 6 wherein the angiostatic agent is selected from the group consisting of 21-methyl-5β-pregnan-3α,11β, 17α, 21-tetrol-20-one 21-methyl ether; 3β-azido-21-acetoxy-5β-pregnan-11β, 17α-diol-20-one; 3β-acetamido-21-acetoxy-5β-pregnan-11β, 17α-diol-20-one; 5β-pregnan-11β, 17α, 21-triol-20-one; 4, 9(11)-pregnadien-17α,21-diol-3,20-dione-21-acetate and 4, 9(11)-pregnadien-17α,21-diol-3,20-dione.

8. The composition of Claim 6 wherein the compound is present at a concentration between 0.005 and 5.0 weight percent.

9. The composition of Claim 7 wherein the compound is 4, 9(11)-pregnadien-17α,21-diol-3,20-dione-21-acetate or 4, 9(11)-pregnadien-17α,21-diol-3,20-dione.

10. The composition of Claim 8 wherein the compound is present at a concentration of between 0.05 and 2.0 weight percent.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/25913

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/57 A61K31/575 A61K31/56

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 91 19731 A (UPJOHN CO) 26 December 1991 see page 4, line 31 see page 15 ---	1-10
X	US 5 371 078 A (CLARK ABBOT F ET AL) 6 December 1994 see column 2, line 38 - line 41 see column 3; figures A,B ---	1-10
X	US 4 876 250 A (CLARK ABBOT F) 24 October 1989 cited in the application see page 4, line 37 - line 50 ---	1-10
X	US 5 698 545 A (CLARK ABBOT F ET AL) 16 December 1997 cited in the application see claims 1-3 --- -/--	1-10

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 May 1999	25/05/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Trifilieff-Riolo, S

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 93 10141 A (ALCON LAB INC) 27 May 1993 see page 5 - page 15 ---	1,2,5,6
A	WO 95 18621 A (UNIV DUKE) 13 July 1995 see page 8, line 15 - line 19 -----	1-10

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/25913

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
In view of the large number of compounds which are defined by the wording of the claims, the search has been performed on the compounds mentioned in the examples of the description.

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 98/25913

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Information on patent family members

Int tional Application No
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